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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/483,337	01/14/2000	Eric T. Kool	220.00040101	8254

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EXAMINER

CRANE, LAWRENCE E

ART UNIT PAPER NUMBER

1623

DATE MAILED: 04/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/483,337	Applicant(s) KOOL, ERIC T.	
	Examiner L. E. Crane	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11/17/03 (amdt).
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 44-48,50-54,56-60 and 64-72 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 44-48,50-54,56-60 and 64-72 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 01/14/02 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>11/17/2003</u> . | 6) <input type="checkbox"/> Other: _____ |

No claims have been cancelled, new claims **64-72** have been added, the disclosure has not been amended, and no claims have been amended as per the amendment filed November 17, 2003. One additional Supplemental Information Disclosure Statements (IDSs) filed November 17, 2003 has been received and made of record.

Claims **44-48, 50-54, 58-60 and 64-72** remain in the case.

The disclosure is objected to because of the following informalities:

Incorporation by reference of essential material by reference to a foreign application or a foreign patent or to a publication inserted in the specification is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by applicant, or a practitioner representing applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

In each of the above cases, the incorporations are of the complete document, and fails to properly point out the particular portions of the US patent(s) being incorporated; see MPEP §608.01(p)(1)(A) noting *In re de Seversky* and in the same paragraph (column 2 of p. 600-769, August 2001 edition) the instruction which reads as follows: “[p]articular attention should be directed to specific portions of the referenced document wherein the subject matter being incorporated may be found.”

In addition, each of the above incorporations represents a failure to provide specific disclosure of how to make and/or use. Therefore, the above citations of the *Hawkins* decisions continue to apply to all incorporations by reference.

The attempt to incorporate subject matter into this application by reference to “all patents publications and electronic publications at page 61, lines 13-15,” is improper because applicant has thus far failed to provide the requisite declarations and amendments wherein essential subject matter has been incorporated from any other reference. In order to make this requirement clear; applicant should also be prepared to provide incorporated amendments for

all US patents and applications, except for applications wherein the benefit of priority has been claimed, as well. Alternatively, applicant may elect to delete the noted sentence.

Appropriate correction is required.

The drawings are objected to because the last circular oligonucleotide (Seq. ID No. 21) in Figure 4A includes a typographical error: a lower case “s” is incorrectly represented by a period (“.”) at the bottom of the representation.

The drawing of the product of “ligation of duplex DNA” (Seq. ID No. 16) in Figure 4A incorrectly illustrates hydrogen bonding between bases in the middle of the paired sequences, apparently because the lower case “s” (added apparently to represent the phosphorothioate linkage) is incorrectly assumed to be a base equivalent.

Correction is required.

Claims **44-48, 50-54, 56-60 and 64-72** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims have not met the written description standard of *Regents of the University of California v. Eli Lilly* (119F.3d 1559 at 1568; 43 USPQ2d 1398 at 1406 (Fed. Cir 1997)) which MPEP §2163 at page 2100-162, column 1, quotes as follows: “A definition by function alone ‘does not suffice’ to describe a coding sequence ‘because it is only an indication of what the gene does, rather than what it is.’” Applicant continues to rely on generic functional terminology including “leaving group” wherein the disclosure definition thereof does not overcome the functionality of the noted term. For example, the leaving group-containing generic class “oligonucleotide containing an α -haloacyl group” is mentioned at page 4, lines 21-22, but the exemplifications are solely directed to 5'-deoxy-5'-iodo-terminated species. Similarly, applicant has mentioned 3'-phosphorotellurate” modified oligonucleotides, but has not provided any examples of this generic class. The noted terms are each lacking a complete written description.

Applicant's arguments with respect to claims **44-48, 50-54 and 56-60** have been considered but are deemed to be moot in view of the new grounds of rejection.

Claims **44-48, 50-54, 56-60 and 64-72** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in *In re Wands* (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988)) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims is over broad because it is defined by terms including "comprising a 5'-leaving group," "phosphorotelluroate," "an oligonucleotide containing an a-haloacyl group," "the 5'-leaving group and the 3'-functional group in close proximity to one another," "substantially adjacent," "gap of 1 or 2 bases," and "overlap of 1 or 2 bases," wherein all but the first three terms make reference to the relative locations of the reactive 3'- and 5'-termini of the oligonucleotides which undergo spontaneous ligation after hybridizing to a longer target oligonucleotide. In addition the term "oligonucleotide probe of less than 7 nucleotides" makes reference to the hybridization of oligonucleotides having lengths of 3, 4, 5 and 6 bases, a class of probes not found in any working example.

B. The nature of the invention is the use of hybridization to determine the presence of a genetic polymorphism by co-hybridization of two terminally reactive oligonucleotides with sequences selected to match the target sequence, and detection of the autoligated product. The termini of the reactive oligonucleotides are claimed to be reactive (undergo ligation) when immediately adjacent, when there is a 1-2 base gap between them or when there is a 1-2 base overlap.

C. The state of the prior art includes multiple reports that auto chemical ligation reaction occurs between co-hybridized oligonucleotides with adjacent reactive termini as disclosed herein. The terminal reactive groups in the prior art are 5'-deoxy-5'-bromo or iodo, or 5'-deoxy-5'-(N-iodoacetylamido), and 3'-phosphorothioate, respectively.

D. The level of one or ordinary skill is high, requiring a knowledge of how to making oligonucleotides with appropriately modified termini and how to conduct hybridizations wherein the presence of the ligated product is detected.

E. The level of predictability in the art is high with regard to situations wherein the reactive groups are adjacent (part of nucleosides hybridized to adjacent bases on the target oligonucleotide), but there is no prior art teaching of reaction occurring when there is either a gap of one or two bases or an overlap of 1 or 2 bases. There is also no prior art teaching of how to incorporate a phosphorotelluroate at the 3'-position of an oligonucleotide or how to use with a species in a chemical ligation process like that claimed herein.

F. The amount of direction provided by the inventor is limited to how to make and use an oligonucleotide including a 3'-phosphorothioate or 3'-phosphoroselenoate and how to make and use an oligonucleotide including only a 5'-deoxy-5'-iodonucleoside in a chemical ligation process. Although the disclosure mentions "an oligonucleotide containing an a-haloacyl group" there is no teaching of which particular subgenus of compounds is being referred to by this term or how to use said subgenus compounds in the instant disclosed process. Similarly there is no mention of how to make or use any leaving group at the 5'-location other than the iodo group. Also there is no teaching of what conditions are observed when ligation occurs across a gap of 1-2 bases or an overlap of one to two bases.

G. The existence of working examples is limited to disclosures of how to make and use an oligonucleotide including a 3'-phosphorothioate or 3'-phosphoroselenoate and how to make and use an oligonucleotide including a 5'-deoxy-5'-iodonucleoside in hybridization-mediated a chemical ligation process and the detection of the ligation product with 7mer and 13mer oligonucleotides, but not with anything shorter than a 7mer.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be excessive. The presence of the noted functional terms and terms which allege processes resulting in ligation wherein there are either gaps or overlaps are deemed to be extrapolations which are not justified by the very limited scope of the instant disclosure. Applicant is respectfully requested to provide claims more narrowly drawn to the scope enabled herein.

Applicant's arguments with respect to claims **44-48, 50-54 and 56-60** have been considered but are deemed to be moot in view of the new grounds of rejection.

Claims **44-48, 50-54, 56-60 and 64-72** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims **44, 50 and 56** at lines 8, 9 and 10, lines 12, 14, 17, 18, 19 and 20 and lines 7, 8 and 9, respectively, the term "comprising" renders the metes and bounds of the claim indefinite, particularly because said term refers to chemically modified starting materials and products and by such reference implies the absence of a complete description of the structural features of said chemically modified starting materials and products. Said term, as a synonym of including, begs the question -- Including what else?-- See also claims **64-72**.

Applicant's arguments filed November 17, 2003 have been fully considered but they are not persuasive.

Applicant alleges that the above rejection is not understood because "it is not clear as to which part of the claim the Examiner is applying the rejection." Examiner has amended the rejection to more particularly point out why the rejection was made, more particularly point out the term to which it is deemed to apply, and the lines in which said term appears in the noted claims. Applicant also argues that "comprising" is an acceptable transitional term. Examiner agrees in part, but in rebuttal argues that this term does not apply to claims or portions of claims directed to chemical structures because said term may be read to imply an incomplete description of the chemical structure; e.g. the claim -- A compound comprising ethanol. -- reads on potable distilled liquors and/or on chemical analogues of ethanol whereas the claim -- A compound having the formula $\text{CH}_3\text{-CH}_2\text{-OH}$.-- is directed only to the compound ethanol and may not be read to include mixtures of ethanol with other substances or to compounds which are structurally related to ethanol.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

"A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent."

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.”

(e) the invention was described in a patent granted on an application to another filed in the United States before the invention thereof by applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.”

Claims **44-48, 50-54, 56-60 and 67-72** are rejected under 35 U.S.C. §102(e) as being anticipated by **Letsinger et al. ‘613** (PTO-1449 ref. **AF**).

Applicant is referred to the abstract, pages 13 and 17 and Figures **1, 5, 9, 12 and 13** wherein the instant claimed invention has been anticipated.

Applicant’s arguments with respect to claims **44-48, 50-54 and 56-60** have been considered but are deemed to be moot in view of the new grounds of rejection.

Claims **44-48, 50-54, 56-60 and 67-72** are rejected under 35 U.S.C. §102(b) as being anticipated by **Northwestern University ‘699** (PTO-1449 ref. **AM**).

Applicant is referred to the abstract at page 1, pages 13 and 17 and Figure **2** wherein the instant claimed invention has been anticipated.

Applicant’s arguments filed November 17, 2003 have been fully considered but they are not persuasive.

Applicant argues that the limitation “less than 7 nucleotides in length” (referring to the length of a reactive oligonucleotide) is “not taught by the prior art.” Applicant’s attention is directed to claim *1* of the **‘699** reference wherein there is no limitation as to the length of any oligonucleotide involved in the claimed chemical ligation process. The absence of any specified length means that **all lengths are covered.** alternatively, if applicant wants examiner to believe that the short (2, 3, 4, 5 and 6) oligos are properly enabled, examiner suggests providing a showing (sworn declaration under 37 C.F.R. § 1.132) that they actually work. As to the term “not directly adjacent,” if applicant means situations wherein there is a “gap” or an “overlap,” examiner also does not see any enabling support for this subject matter herein so the assertions of applicant are found to be lacking is enabling support also (declaration would be inappropriate(new matter) as examiner fails to find any examples herein wherein either a gap or overlap situation has been shown by applicant to actually work). For the situations wherein

there is no gap or overlap (directly adjacent), the subject matter appears to have been anticipated (see new grounds of rejection *supra*).

Claims **44-48, 50-54, 56-60 and 67-72** are rejected under 35 U.S.C. §102(b) as being anticipated by **Letsinger et al. '943** (PTO-1449 ref. AC).

Applicant is referred to claims **1 and 5** at columns 15-16 wherein the instant claimed process is anticipated in its entirety.

Applicant's arguments filed November 17, 2003 have been fully considered but they are not persuasive.

Applicant is referred to comments in response following rejections citing the **'699** reference.

Claims **44-48, 50-54, 56-60 and 67-72** are rejected under 35 U.S.C. §102(b) as being anticipated by **Gryaznov et al. '903** (PTO-1449 ref. AB).

Applicant is referred to the abstract, to claims **1-13**, and to column 10 at lines 3-4 which together anticipate the instant claimed process.

Applicant's arguments filed November 17, 2003 have been fully considered but they are not persuasive.

Applicant is referred to comments in response following rejections citing the **'699** reference.

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made."

Claims **44-48, 50-54, 56-60 and 67-72** are rejected under 35 U.S.C. §103(a) as being unpatentable over **Northwestern University '699** (PTO-1449 ref. AM).

The instant claims are directed to a process of autoligation wherein autoligating oligonucleotides bind to a target solid-supported linked oligonucleotide target and when hybridization takes place under relatively non-stringent conditions the autoligating probes which hybridize in a sequence specific manner with the target undergo chemical autoligation forming a new oligonucleotide which is then subsequently detected as an indication of the presence of the target sequence.

Northwestern University '699 in claims *1 and 5* discloses the autoligation process claimed herein.

Northwestern University '699 does not expressly disclose the particular target oligonucleotide or details of the oligonucleotide sequence to be autoligated to.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the instant disclosed process to any solid-supported target including the targets taught by the instant claims. Any variations required to achieve a working test process with a different target sequence are deemed to have been within the purview of the ordinary practitioner seeking to optimize the prior art process, in the absence of a clearly convincing showing of unexpected results.

Therefore, the instant claimed hybridization-based method of oligonucleotide sequence detection would have been obvious to one of ordinary skill in the art having the above cited reference before him at the time the invention was made.

Applicant's arguments filed November 17, 2003 have been fully considered but they are not persuasive.

Applicant's notice of the interview is noted. Examiner, upon reconsideration, has concluded that the absence of any limitations in the claims of the '699 reference means that all lengths of reactive oligonucleotides are covered and for this reason withdraws the previous finding of allowability. However, the rejected claims are limited to those wherein adjacent reactive substituents are specifically excluded by applicant's limitation. As to applicant's limitations concerning particular target oligonucleotides ("genetic polymorphism," etc.), there has been no showing of unexpected results herein, and therefore examiner concludes that the prior art includes these possible alternatives even when not particularly specified because to

find otherwise would be to unfairly impinge on the scope of previously granted patent claims. As to applicant's arguments concerning failure to meet all limitations, examiner notes that applicant has failed to particularly point out any patentably distinguishing feature by identification in any claim of one or more particular structural differences with the prior art.

Claims **64-66** would be allowable if rewritten or amended to overcome the rejection under 35 U.S.C. 112.

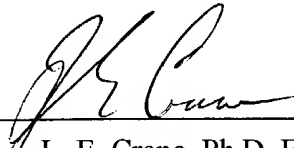
Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX (unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 703-872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at **571-272-0661**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec
06/19/03



L. E. Crane, Ph.D. Esq.
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